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Pulsed Dye Laser Therapy for Sun Damaged Skin

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Objective: **The objective of this study was to evaluate the effectiveness of the pulsed dye laser (585 nm, 450 ms) in the treatment of sun induced wrinkles.**
Design: **Patients had one pulsed dye laser (585 nm) treatment. The treated areas were assessed by the following methods: grading of skin wrinkles at 6 weeks, 12 weeks, and 6–14 months after treatment by blinded observers and by light and electron microscopy.**
Setting: **An ambulatory care center at Abbott Northwestern Hospital (ANH) and the Laser & Skin Surgery Center of Northern California (LSSCNC).**
Patients: **Twenty patients were treated, half with mild to moderate and half with moderate to severe sun induced skin wrinkles.**
Results: **At last follow up 90% (9/10) of the mild to moderate wrinkles and 40% (4/10) of the treated patients with moderate to severe wrinkles had clinically observable improvement in their sun induced skin wrinkles. Histologic examinations of the treated areas showed a superficial dermal band of well organized elastin and collagen fibers replacing pre-treatment elastic tissue. Increased cellularity and mucin deposition was consistent with dermal collagen remodeling. Lasers Surg. Med. 25:229–236, 1999.** **© 1999 Wiley-Liss, Inc.**

Key words: pulsed dye laser; wrinkles; skin

INTRODUCTION

Wrinkling, coarseness, irregular pigmentation, and skin cancers are all clinical signs of cutaneous photodamage [1,2,3]. Ultraviolet light can also lead to microscopic changes detected within the epidermis and dermis. The epidermis changes in thickness and individual keratinocytes become atypical in appearance and disorganized. Dermal elastin and fibrillin fibers increase in quantity and form clumps in the superficial dermis. Whereas anchoring fibrils become decreased, superficial collagen fibers become disorganized and basophilic when examined microscopically. These changes all give rise to the clinical signs of photoaging.

There are several methods used to treat photodamaged skin. Topical treatment with tretinoin

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cream has shown to be effective for treating the clinical signs of photodamaged skin [4]. For more severe sun damage, chemical peels, dermabrasion, and laser resurfacing successfully [5] remove or destroy the top layers of skin, allowing the growth of new nonphotodamaged skin. These more aggressive methods are associated with prolonged discomfort and healing time, lasting from 10 days to several months, and the risk of scarring [6].

The pulsed dye laser (PDL) delivers yellow light (585 nm) that is well absorbed by superficial blood vessels. These targeted vessels are destroyed by selective photothermolysis leaving surrounding structures uninjured. The PDL is commonly used to treat port wine stains, hemangiomas [7,8], telangiectasia, and other vascular anomalies. More recently its been shown that striae distensa, which have abnormal collagen and elastin, can be effectively treated with the pulsed dye laser [9]. After treatment with the PDL, the clinical appearance of atrophic striae distensa can be improved or even disappear and histologic examinations show new deposition of normal elastic fibers. Recent studies have also shown improvement in pruritus, tenderness, and in skin texture of hypertrophic scar tissue after PDL treatments [7,10,11]. This apparent effect on dermal collagen suggests a possible role for PDL in the treatment of wrinkles. In addition, anecdotal observations of improved periorbital wrinkling in patients treated with PDL for facial vessels prompted each center independently to investigate this further.

PURPOSE

The overall purpose of this study was to evaluate the effectiveness of the pulsed dye laser (585 nm, 450 ms) in the treatment of sun induced wrinkles.

STUDY DESIGN

Initially performed as two independent and separate studies, the data was combined to increase the validity of the study. Twenty patients with mild to severe sun induced facial wrinkles were selected by screening adult volunteers who answered an ad in the local newspaper or who were currently patients at one of our facilities. Ten patients had mild to moderate wrinkles (LSSCNC) and 10 patients had moderate to severe wrinkling (ANH). All volunteers under 18 years of age, pregnant, excessively tanned or dark skinned were excluded. Each center (ANH and LSSCNC) completed their study independently and pooled their results after they learned of each other's similar efforts.

MATERIALS AND METHODS

Informed consent was obtained from each patient after the study was thoroughly explained. The test areas were photographed prior to each treatment and at 6 weeks, 12 weeks, and/or 6 to 14 months after treatment. All patients received one treatment to the perioral or periorbital region with a pulsed dye laser (585 nm, 450 ms) (Photogenica V, Cynosure, Chelmsford, MA, at ANH and SPTL-1b, Candela, Wayland, MA, at LSSCNC) (Table 1A,B). A 7 or 10 mm spot size with 3.0–6.5 J/cm^2 energy density was used overlapping 10–15% as noted by immediate purpura. Some of the patients (ANH) were treated through a Vigilon® dressing. Aloe vera gel or antibiotic ointment was applied immediately after treatment. The patients continued to apply antibiotic ointment if any blistering or crusting developed.

At the LSSCNC the percent clearance of the treated areas was recorded by three blinded observers on a scale of 0 to 4, where 0 represents no clearance, 4 represents total clearance, and intermediate values represent intervals of 25%. Biopsies of treated and non-treated areas were taken from three patients at 6 and/or 12 weeks.

At ANH the degree of wrinkling was evaluated by three blinded observers examining projected 35 mm slides on a scale of 1 to 5 where 1 through 5 represents no, mild, moderate, moderate to severe, and severe wrinkling respectively. There scores were then averaged. Each volunteer patient also had a 3 mm skin biopsy taken prior to treatment and at 12 weeks after treatment. The skin biopsies were evaluated under light and/or electron microscopy.

RESULTS

Clinical

The clinical results are detailed in Table 1. Nine out of 10 patients with mild to moderate wrinkling treated at the LSSCNC showed 50% (Fig. 1) or more improvement with 3/10 showing 75% or greater improvement. All patients maintained their level of improvement for 6 months as did 5/6 patients checked at 12 months post treatment. One out of 6 had dropped one gradation level.

TABLE 1. Patient Data and Clinical Results From ANH

Patient #	Age	Sex	Skin type[1]	Spot size	J/cm2	Vigilon®	Area tx	Pre-Tx grade	% Change 3 mo.	% Change 14 mo.
1	59	F	III	10	4	No	R perioral	3.8	0	–21
				10	5	Yes	L perioral	3.6	0	–16
2	45	F	II	10	4	No	R perioral	5	0	28
				10	5	Yes	L perioral	4.8	0	38
3	55	F	II	10	3	No	R periorbital	3.8	0	11
				10	4	Yes	L periorbital	3.8	0	21
4	49	F	II	10	3	No	R periorbital	4	14.9	20
				10	4	Yes	L periorbital	4.6	14	26
				10	4	No	R perioral	3.8	7	0
				10	5	Yes	L perioral	4	0	10
5	72	F	II	10	3	No	R periorbital	4.6	0	4
				10	4	Yes	L periorbital	5	7	12
				10	4	No	R perioral	2.6	9.1	8
				10	5	Yes	L perioral	3.2	0	25
6	70	M	III	10	3	No	R periorbital	5	0	0
				10	4	Yes	L periorbital	5	0	–10
				10	4	No	R perioral	2.8	0	–7
				10	5	Yes	L perioral	2.8	0	–7
7	61	F	II	10	3	No	R periorbital	2.8	17.5	–36
				10	4	Yes	L periorbital	3.2	–8.1	–6
8	46	F	II	10	3	No	R periorbital	0.6	0	x[2]
				10	4	Yes	L periorbital	0.7	0	x
9	61	F	III	10	4	No	R perioral	3.6	–4.1	x
				10	5	Yes	L perioral	3.7	0	x
10	64	F	II	10	4	Yes	R periorbital	3.1	0	x
				10	3	No	L periorbital	3.1	–6.4	x
				10	4	Yes	R perioral	3.1	0	x
				10	3	No	L perioral	3.1	–6.4	x

[1]Fitzpatrick.
[2]x, no follow-up; (–), progression of wrinkling.

TABLE 1B. Patient Data and Clinical Results From LSSCNC

Patient #	Age	Sex	Skin type[1]	Spot size	J/cm2	Treated area	% Imp 3 mo.	% Imp 6 mo.	% Imp 12 mo.
11	38	F	II	7	6.5	Periorbital	50	x[2]	x
12	30	F	II	7	6	Periorbital	75	75	x
13	42	F	II	7	6	Periorbital	50	50	50
14	42	F	II	10	5	Periorbital	50	50	50
15	40	F	II	10	5	Periorbital	50	50	50
16	37	F	II	10	5	Periorbital	75	75	50
17	58	F	III	10	5	Periorbital	50	50	50
18	39	F	II	10	5	Perioral	75	75	75
19	41	F	II	10	5	Periorbital	75	x	x
20	40	F	II	7	6	Periorbital	20	x	x

[1]Fitzpatrick.
[2]x, no follow-up.

In contrast, 12 weeks after treatment three of the 10 with moderate to severe wrinkling at ANH had clinically observable improvement. Seven of the original 10 patients were available for follow-up 14 months after treatment. Four of these patients had clinically observable improvement from 4 to 38% (Fig. 2), although three patients were noted to have progression of their wrinkling. Analysis of the percent clearance as graded by blinded observers showed no statistically significant changes in the amount of skin wrinkling after treatment.

Side effects of the treatment included purpura and swelling (Fig. 1B), which occurred in all subjects and lasted from 1 to 2 weeks. Two subjects had postinflammatory hyperpigmentation that cleared with hydroquinone and sunscreen therapy.

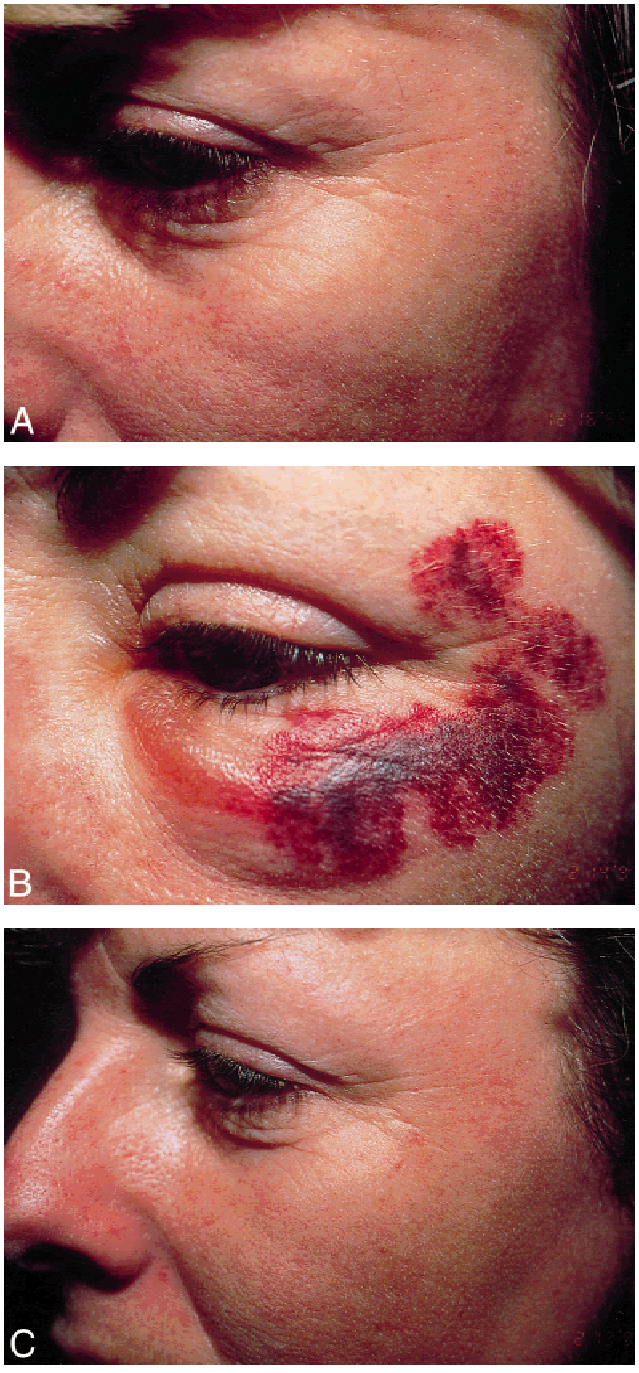

Fig. 1. Clinical appearance of laser treated skin. Clinical appearance of patient #15 prior to (**A**) 2 days after (**B**) and 6 months after (**C**) PDL treatment. Note untreated wrinkle, as evidenced by lack of purpra in Figure B, shows lack of improvement in contrast to surrounded treated wrinkles graded as 50% improvement.

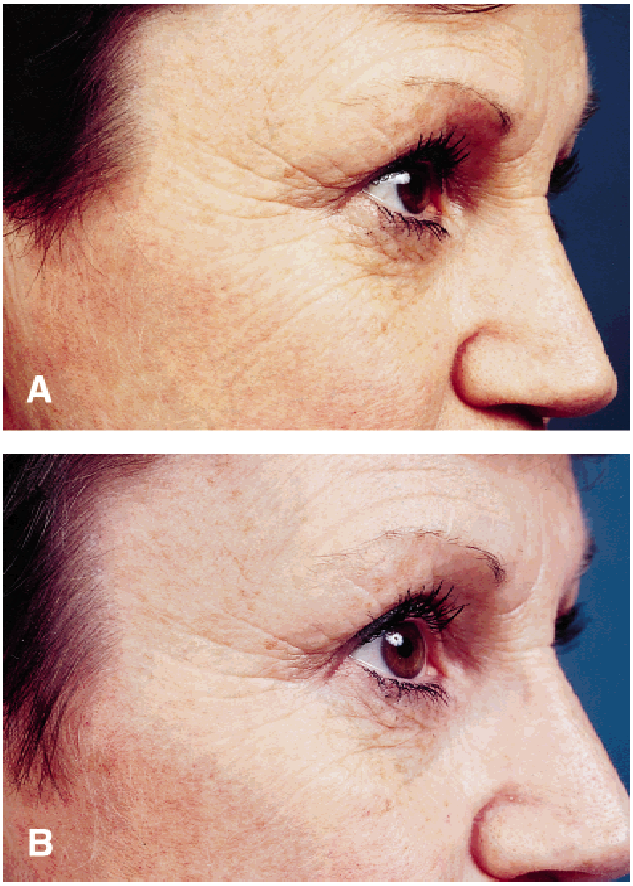

Fig. 2. Clinical appearance of laser treated skin. Clinical appearance of patient #4 prior to (**A**) and 14 months after (**B**) PDL treatment.

Histology

Examination of the biopsies taken at 6 and 12 weeks after treatment under light microscopy revealed a thickened stratum spinosum and a thickened layer of normal staining collagen within the superficial dermis (Fig. 3). Also seen is an increase amount of mucin deposition in the superficial dermis and a downward compression of the basophilic connective tissue.

Ultrastructural evaluation of the treated samples compared to non-treated samples from ANH showed an increased amount of normal appearing elastic and collagen fibers within the superficial dermis (Fig. 4). Treated areas showed a decrease in clumping of degenerated elastic fibers within the superficial dermis. Active fibroblasts were detected in the 12 week post treated samples (Fig. 5). Changes in anchoring fibrils, desmosomes, and hemidesmosomes could not be detected in the samples examined.

DISCUSSION

This study shows that clinical wrinkling and histologic effects of sun induced skin changes can be improved by PDL treatment. More than half of

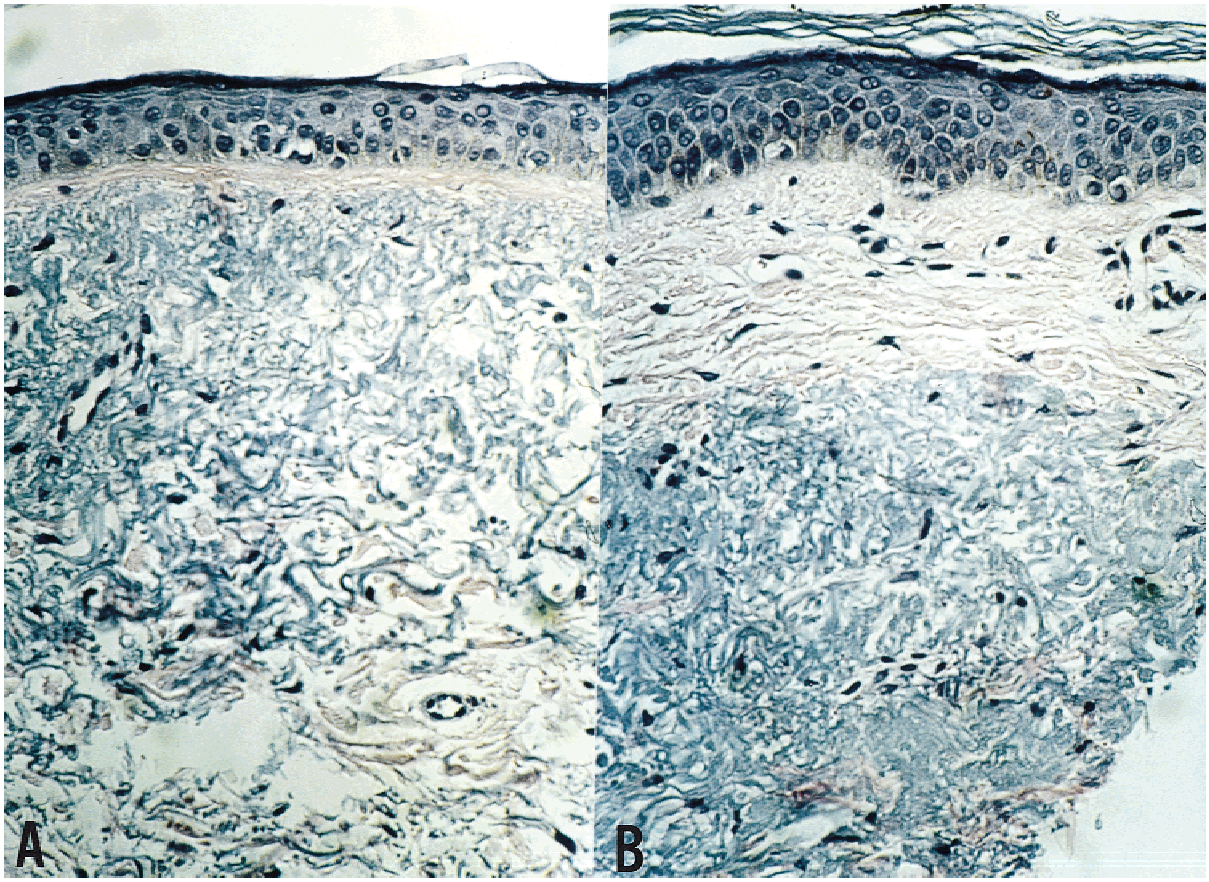

Fig. 3. Light microscopy of laser treated connective tissue. Biopsies taken prior to (**A**) and 12 weeks after (**B**) pulsed dye laser treatment. Note thin disorganized epidermis and elastotic dermal connective tissue extending to the epidermal-dermal junction in the pre-treatment biopsy A. After treatment the epidermis became thicker and more organized and a thickened grenz zone of normal staining connective tissue is seen extending down from the basement membrane zone B. (H & E, 205×).

the patients demonstrated clinical improvement with one PDL treatment, 90% of those with mild wrinkling improved 50% or more with several patients having near resolution of their wrinkles. Those with severe wrinkles did not have as much clinical improvement.

This discrepancy may be exaggerated by the different scoring methods performed at each center. At the LSSCNC, where the patients had mild wrinkling, the treated and non-treated images were viewed simultaneously with the graders scoring percent improvement while knowing which area was treated. At ANH, where most of the patients had moderate to severe wrinkling, the pre- and post treatment images were viewed simultaneously, yet the graders scored the amount of wrinkling in each image while being blinded to which were pre- and post treatment. In contrast to the clinical results, histologic improvement was noted in all cases with greatest improvement noted in more severely photodamaged skin.

The mechanism for normalizing actinically damaged or scarred skin is a complex problem most likely involving multiple processes and produced by a variety of techniques. Many studies have demonstrated the effects of topical preparations including retinoic acid, alpha hydroxy acids, and vitamin C derivatives on photodamaged skin [12–14]. Aside from these pharmaceutical therapies, physical injury to the skin and removal of the epidermis and superficial dermis as seen with chemical peels, ultrasound, electrical stimulation, dermabrasion, and ablative laser resurfacing have all showed enhanced wound healing and normalization of scarred and photodamaged skin [15–21].

Recent studies using near infrared lasers have detected some clinical improvement of sun damage skin [20,21]. The systems used in these studies had pulse durations from the nanosecond to millisecond domain as well as wavelengths with much less hemoglobin absorption than the

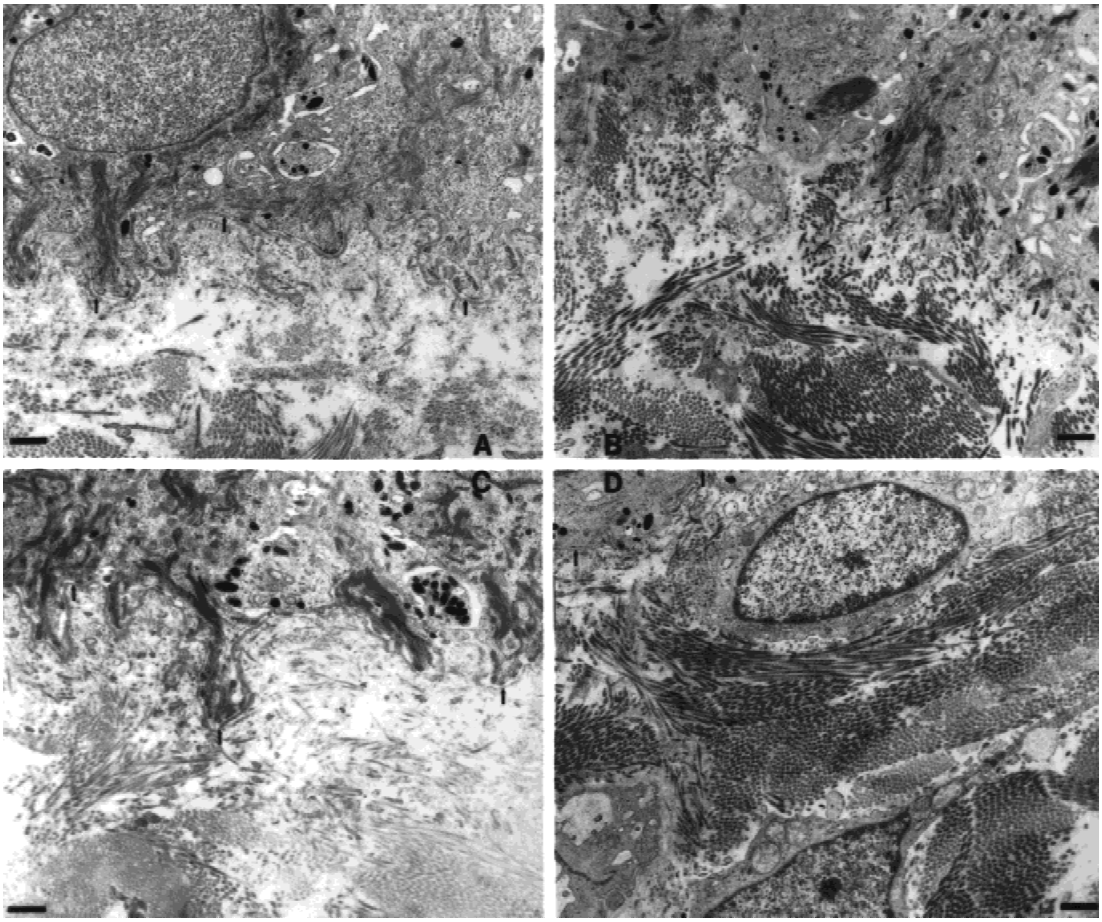

Fig. 4. Electron microscopy of laser treated connective tissue. Patient #1 showing sparse disorganized collagen before treatment **(A)**, Patient #1 showing organized new collagen formation 12 weeks after PDL treatment **(B)**, Patient #2 showing sparse disorganized collagen before treatment **(C)**, Patient #2 showing organized new collagen formation 12 weeks after PDL treatment **(D)**. Small arrows point to the basement membrane. (15,500× Bar = 1 micron).

585 nm pulsed dye laser that was used in our study. These lasers do have a greater absorption coefficient for collagen than the pulsed dye laser (585 nm) suggesting that direct injury or temperature change of collagen may lead to similar clinical endpoints. However, selectively targeting the superficial dermal vasculature with the PDL may offer some advantages. Treatment with the PDL can not only normalize hyper-proliferative cutaneous processes such as psoriasis and hypertrophic scars but also atrophic processes seen in stria distensia [7,9–11,22,23]. These responses taken together suggest that a variety of cutaneous interventions can lead to a similar clinical endpoint and that the same intervention in different clinical situations can result in opposite effects.

To narrow down the complex process of wound healing and cutaneous regeneration there are several mechanisms in which PDL treatment many normalize photodamaged skin. From the histologic examination there was an increase in epidermal thickness and keratinocyte organization, along with increased production of superficial organized collagen and elastin, pushing elastotic connective tissue deeper into the dermis, without apparent changes in anchoring fibrils or prolonged inflammatory cell changes. Possible mechanisms for these findings include a direct vascular injury and resultant ischemic or thermal effect leading to injury/stimulus of perivascular structures, an epidermal or dermal cell specific injury/stimulus, a vascular leakage leading to elaboration of blood components into the dermis, or an epidermal injury by melanin absorption of PDL light, all of which lead to a reparative response.

This study did not examine the acute inflammatory or proliferative events directly after treatment, which may help elaborate the mechanisms involved. A series of biopsies taken at various time points after treatment with examination for

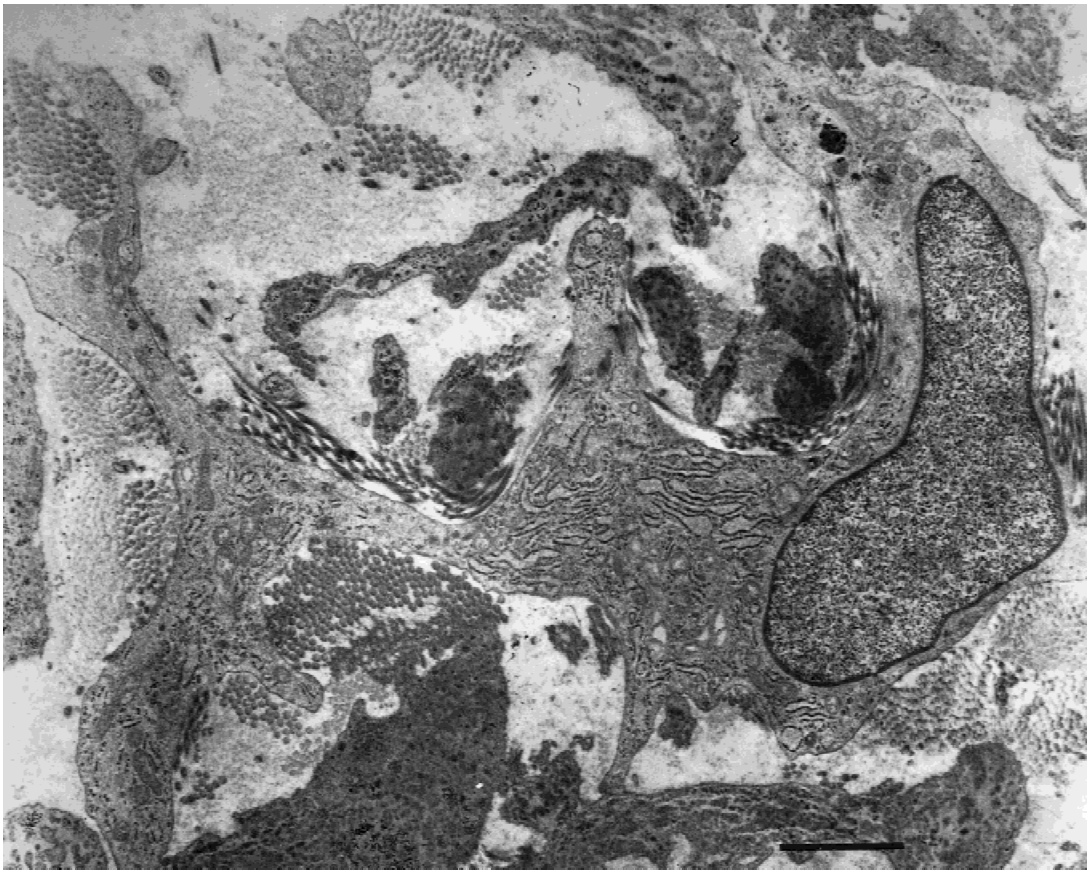

Fig. 5. Electron microscopy of post treatment fibroblast creating collagen. Fibroblast with large amount of rough endoplasmic reticulum generating new connective tissue 12 weeks after PDL treatment. (18,500× Bar = 1 micron).

specific cellular components, growth factors, and cytokines would help to elaborate the events leading to the histologic changes.

The major side effect of this treatment is the significant bruising and swelling seen after treatment, which lasts up to 2 weeks. This may be alleviated by using much lower fluences and retreating at various intervals. In conclusion, PDL treatments offer some promise for patients with mild skin changes or mild wrinkling.

REFERENCES

1. Bernstein EF, Chen YQ, Tamai K, et al. Enhanced elastin and fibrillin gene expression in chronically photodamaged skin. Journal of Investigative Dermatology 1994; 130:182–186.
2. Uitto J, Fazio MJ, Olsen DR. Molecular mechanisms of cutaneous aging. J Am Acad Dermatology 1989;21:614–622.
3. Warren R, Gartstein V, Kligman AM, Montagna W, Allendorf RA, Ridder GM. Age, sunlight, and facial skin: a histologic and quantitative study. J Am Acad Dermatology 1991;25:751–760.
4. Gilchrest BA. Treatment of photodamage with topical tretinoin: an overview. J Am Acad Dermatol 1997;36(3 Pt 2):S27–36.
5. Fitzpatrick RE, Goldman MP, Satur NM, Tope WD. Pulsed carbon dioxide laser resurfacing of photoaged skin. Arch Dermatol 1996;132:395–402.
6. Lowe NJ, Lask G, Griffin ME, Maxwell A, Lowe P, Quilada F. Skin resurfacing with the Ultrapulse carbon dioxide laser: observations on 100 patients. Dermatologic Surgery 1995;21(12):1025–1029.
7. Alster TS, Kurban AK, Grove GL, Grove MJ, Tan OT. Alteration of argon laser induced scars by the pulsed dye laser. Lasers Surg Med 1993;13:368–373.
8. Ashinoff R, Geronemus RG. Flashlamp-pumped pulsed dye laser for port wine stains in infancy: earlier versus later treatment. J Am Acad Dermatology 1991;24:467–472.
9. McDaniel DH, Ash K, Zukowski M. Treatment of stretch marks with the 585 nm flashlamp-pumped pulsed dye laser. Dermatologic Surgery 1996;22:332–337.
10. Alster TS. Improvement of erythematous and hypertrophic scars by the 585 nm flashlamp-pumped pulsed dye laser. Annals of Plastic Surgery 1994;32:186–190.
11. Alster TS, Williams CM. Treatment of keloid sternotomy scars with 585 nm flashlamp-pumped pulsed dye laser. Lancet 1995;345:1198–1200.
12. Lewis AB, Gendler EC. Resurfacing with topical agents.

Seminars in Cutaneous Medicine & Surgery 1996;15(3): 139–144.
13. Kligman AM. Topical retinoic acid (tretinoin) for photoaging: conceptions and misperceptions. Cutis 1996;57(3): 142–144.
14. Ellis CN, Weiss JS, Hamilton TA, Headington JT, Zelickson AS, Voorhees JJ. Sustained improvement with prolonged topical tretinoin (retinoic acid) for photoaged skin. J Am Acad Dermatology 1990;23(4 Pt 1):629–637.
15. Conlan MJ, Rapley JW, Cobb CM. Biostimulation of wound healing by low-energy laser irradiation. A review. Journal of Clinical Periodontology 1996;23(5):492–496.
16. Gum SL, Reddy GK, Stehno-Bittel L, Enwemeka CS. Combined ultrasound, electrical stimulation, and laser promote collagen synthesis with moderate changes in tendon biomechanics. American Journal of Physical Medicine & Rehabilitation 1997;76(4):288–296.
17. Taskan I, Ozyazgan I, Tercan M, Kardas HY, Balkanli S, Saraymen R, Zorlu U, Ozugul Y. A comparative study of the effect of ultrasound and electrostimulation on wound healing in rats. Plastic & Reconstructive Surgery 1997;100(4):966–972.
18. Harmon CB, Zelickson BD, Roenigk RK, Wayner EA, Hoffstrom B, Pittelkow MR, Brodland DG. Dermabrasive scar revision. Immunohistochemical and ultrastructural evaluation. Dermatologic Surgery 1995;21(6):503–508.
19. Fitzpatrick RE, Goldman MP, Satur NM, Tope WD. Pulsed carbon dioxide laser resurfacing of photo-aged facial skin. Archives of Dermatology 1996;132(4):395–402.
20. Goldberg DJ, Whitworth J. Laser skin resurfacing with the Q-switched Nd:YAG laser. Dermatologic Surgery 1997;23(10):903–906; discussion 906–907.
21. Milner TE, Anvari B, Smithies DJ, et al. Analysis of nonablative skin resurfacing. SPIE Proc 1997:2970.
22. Ros AM, Garden JM, Bakus AD, Hedblad MA. Psoriasis response to the pulsed dye laser. Lasers Surg Med 1996;19(3):331–335.
23. Zelickson BD, Mehregan DA, Wendelschfer-Crabb G, Ruppman D, Cook A, O'Connell P, Kennedy WR. Clinical and histologic evaluation of psoriatic plaques treated with a flashlamp pulsed dye laser. J Am Acad Dermatology 1996;35(1):64–68.